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FMDV-induced stress granules are disrupted by the viral L-protease

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Eukaryotic cells respond to environmental stress by entering a state of reduced protein synthesis, redirecting resources to damage control and defense. This reduced translation is closely linked to the formation of cytoplasmic stress granules (SGs). SGs are multicomponent foci, which contain stalled translation preinitiation complexes, including polyadenylated mRNAs, and several aggregation-prone RNA binding factors, such as the Ras-GAP SH3 domain-binding protein (G3BP) that enable their formation. Once the stress is lifted, the stalled complexes from the SGs are believed to re-engage in translation, facilitating cellular recovery.

A growing body of evidence shows that various viruses can trigger SG formation. However, the presence of SGs may not be beneficial to the virus and many viruses have found ways to circumvent, disrupt or even utilize these granules, suggesting a role for SGs as a general cellular defense mechanism. For picornaviruses, poliovirus have been shown to disrupt SGs by the 3C-protease dependent cleavage of G3BP (3) and for cardioviruses (Theiler's murine encephomyelitis virus and mengovirus), SG formation is inhibited by the presence of the viral L-protein (1, 2).

We have found that foot-and-mouth disease virus (FMDV) triggers SG formation early during infection in IBRS-2 cells. These SGs contain G3BP and TIA-1, but not dsRNA. However, the presence of the FMDV-induced SGs is transient due to the cleavage of G3BP by the viral L-protease (Lpro), which results in subsequent SG dispersal. Cells infected with an Lpro-deficient mutant FMDV are not subjected to G3BP cleavage and the SGs formed upon infection with this mutant maintain throughout the infection. *In vitro* studies using different variants of the Lpro show different G3BP cleavage efficiencies, suggesting a superior function of the full length Lpro for this substrate. Furthermore, the Lpro-directed G3BP cleavage is not dependent on virus replication, as investigated by transfecting FMDV RNAs lacking a functional 3D-polymerase. Finally, FMDV RNAs that contain Lpro, but lack the FMDV 3C-protease, also induce cleavage of G3BP, showing that both FMDV and poliovirus target the same SG component but with different proteases.

References

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